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· 综述 ·

黄嘌呤氧化还原酶抑制剂对牙周炎的治疗潜力研究进展

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【摘要】 牙周炎与嘌呤代谢异常有关,表现为宿主血尿酸增多和牙周组织中的嘌呤降解酶——黄嘌呤氧化还原酶(xanthine oxidoreductase, XOR)表达增加。在病理条件下XOR和尿酸都是促氧化、促炎症介质。动物实验发现,注射尿酸促进牙周炎进展,非布司他(一种XOR抑制剂)可改善牙周炎的组织破坏,阻断尿酸来源可能是一种控制牙周炎进展的治疗策略。本文旨在对XOR抑制剂作为牙周炎潜在治疗药物的合理性进行综述。文献复习结果提示,XOR抑制剂显示出抗氧化、抗炎和抗破骨作用;而且,XOR抑制剂在治疗感染性、炎症性和溶骨性疾病方面显示出临床效果;目前虽无直接证据支持XOR抑制剂对牙周微生态失调有改善作用,但其可调节肠道菌群失调,且有间接证据支持XOR抑制剂对牙周微生态失调的有利作用。综上,XOR抑制剂有可能作为一种免疫调节剂,通过抑制炎症、氧化应激反应和抗破骨作用,对牙周炎起到辅助治疗作用。

【关键词】 牙周炎; 宿主免疫调节; 嘌呤分解代谢; 降尿酸药物; 黄嘌呤氧化还原酶抑制剂; 非布司他; 别嘌呤醇; 炎症; 氧化应激

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Research advances in the therapeutic potential of xanthine oxidoreductase inhibitors for periodontitis LI Yongshan, WU Zhicong, WANG Zixing, YU Xihuang, LIU Xi, YU Ting. Department of Periodontics, School and Hospital of Stomatology, Guangzhou Medical University, Guangdong Engineering Research Center of Oral Restoration and Reconstruction, Guangzhou Key laboratory of Basic and Applied Research of Oral Regenerative Medicine, Guangzhou 510182, China

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【Abstract】 Periodontitis is associated with abnormal purine metabolism, which is manifested by increased uric acid in host blood and increased expression of the purine-degrading enzyme, xanthine oxidoreductase (XOR), in periodontal tissues. Both XOR and uric acid are pro-oxidative and pro-inflammatory mediators under pathological conditions. Animal studies have found that injection of uric acid promotes the progression of periodontitis and that febuxostat (an XOR inhibitor) improves tissue destruction in periodontitis. Therefore, blocking the source of uric acid may be a therapeutic strategy to control the progression of periodontitis. In this article, the rationality of XOR inhibitors as potential therapeutic drugs for periodontitis is reviewed. The literature review results suggest that XOR inhibitors show antioxidative, anti-inflammatory, and anti-osteoclastic effects, and XOR inhibitors show clinical efficacy in the treatment of infectious, inflammatory and osteolytic diseases. Although there is no direct evidence to support the finding that XOR inhibitors can ameliorate periodontal microecological dysbiosis, these drugs can modulate intestinal microflora dysbiosis, and there is

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indirect evidence to support a beneficial effect of XOR inhibitors on periodontal microecological dysbiosis. In conclusion, XOR inhibitors may be used as immunomodulators for the adjuvant treatment of periodontitis by inhibiting inflammation, oxidative stress and anti-osteoclast effects.

【Key words】 periodontitis; host immune modulation; purine catabolism; urate-lowering drugs; xanthine oxidoreductase inhibitors; febuxostat; allopurinol; inflammation; oxidative stress

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牙周炎是导致牙周组织破坏的慢性感染性炎症性疾病,也是全球第六大常见疾病,全球约有11亿人口罹患重度牙周炎。牙周组织破坏程度取决于宿主免疫反应,后者可受环境和遗传因素的影响。机械性清创去除菌斑和牙石是治疗牙周炎的主要方法。然而,对于与遗传或环境因素相关的重度或难治性牙周炎,宿主免疫调节可能有助于控制牙周炎的进展或复发。研究显示,牙周炎与嘌呤代谢异常有关,表现为宿主血尿酸(嘌呤分解的终产物)增多和牙周组织中的嘌呤降解酶——黄嘌呤氧化还原酶(xanthine oxidoreductase, XOR)表达增加^[1]。阻断尿酸来源和促进尿酸的排泄似乎有利于改善牙周炎^[2-3]。本文旨在对 XOR 抑制剂作为牙周炎潜在治疗药物的合理性进行综述。

1 嘌呤代谢、XOR 与牙周炎

近期研究表明,尿酸与牙周病有关。例如,痛风患者罹患牙周炎的风险显著增加^[4],患牙周炎的人或小鼠血尿酸水平升高^[5]。牙周治疗则降低牙周炎患者的血尿酸水平^[6]。此外,牙周病患者唾液和龈沟液中的黄嘌呤(嘌呤分解代谢的底物)含量增加^[7]。牙周炎患者的龈沟液中嘌呤分解代谢加速,且牙龈组织中的嘌呤降解酶 XOR 基因表达增加^[1]。体外实验发现,牙周致病菌成分可刺激巨噬细胞的 XOR 活化并分泌尿酸^[8]。在一定条件下,尿酸和 XOR 都是促氧化介质,诱导活性氧(reactive oxygen species, ROS)的产生^[9]。过量 ROS 则进一步激活炎症信号因子,如活化炎症小体 NOD 样受体热蛋白结构域相关蛋白 3(NOD-like receptor thermal protein domain associated protein-3, NLRP3),最终导致组织损伤^[2]。反之,腹腔注射尿酸也可加重牙周炎小鼠的牙槽骨破坏^[10]。XOR 抑制剂通过

在 XOR 的钼蝶呤(molybdopterin, Mo-pt)结构域与底物(嘌呤或辅酶 I)竞争性结合发挥作用,其中以最经典的 XOR 抑制剂为例:别嘌呤醇主要抑制 XOR 的还原酶形式——黄嘌呤脱氢酶(xanthine dehydrogenase, XDH);非布司他可同时抑制 XOR 的氧化酶——黄嘌呤氧化酶(xanthine oxidase, XOD)和还原酶形式。动物实验表明非布司他(一种降尿酸药物)可抑制牙周炎大鼠的牙龈组织炎症、减少牙槽骨吸收,还可改善伴高尿酸血症的牙周炎患者的牙周临床指标并降低血清炎症因子水平^[2-3]。苯溴马隆(一种尿酸促排药)同样可减轻伴高尿酸血症的牙周炎患者的血清炎症因子反应^[11]。综上, XOR 的活化和尿酸产量的增加与牙周炎的发展有关,阻断尿酸来源和促进尿酸的排泄似乎有利于改善牙周炎。

2 XOR 抑制剂的抗氧化作用

氧化应激在牙周炎致病中发挥着重要的作用:不能被抗氧化防御系统平衡的 ROS 一方面直接引起组织损伤(自由基的脂质过氧化、DNA 损伤、蛋白质损伤、酶氧化),另一方面作为炎症的信号分子或介质,参与牙周炎的发生发展^[12]。实验表明,存在于豆制品中的染料木素可以通过抗氧化的作用改善小鼠牙周炎的损伤^[13]。通过对 32 例 1 型糖尿病患者牙周炎治疗前后的对比,发现血清、唾液、龈沟液中的氧化应激指数明显降低^[14]。别嘌呤醇和非布司他都可以减少 XOR 来源的 ROS 和尿酸,发挥抗氧化作用^[15]。非布司他可改善牙周炎大鼠的牙槽骨吸收,减少牙周组织氧化应激产物的形成如 8-羟基脱氧鸟苷^[2]。鉴于氧化应激是牙周炎的重要致病机制, XOR 抑制剂可能通过抗氧化作用改善牙周炎。

3 XOR抑制剂的抗炎症作用

牙周炎是固有免疫和适应性免疫失调导致的炎症性破坏性疾病,以牙周组织炎症为特征,且可导致系统性炎症。巨噬细胞是主导牙周炎的炎症发生、慢性化、消退的关键细胞^[16]。在免疫细胞中,巨噬细胞是XOR的主要来源,淋巴细胞的XOR表达较低。XOR和尿酸可激活多种炎症信号通路,利用如炎症小体NLRP3通路、p38丝裂原活化蛋白激酶(mitogen-activated protein kinases, MAPK)、Jun蛋白激酶(Jun kinases, JNKs)等,促进巨噬细胞M1向极化^[9]。动物实验发现,别嘌呤醇和非布司他可抑制巨噬细胞M1表型分化,从而抑制促炎因子如TNF- α 的表达^[17]。伴高尿酸血症的慢性牙周炎患者($n=114$)使用碳酸氢钠片和替硝唑片连续治疗1个月,试验组($n=57$)在治疗基础上口服非布司他片(80 mg/d),牙周各项指标试验组相比未服用非布司他片的对照组($n=57$)有更明显的改善,且血清中肿瘤坏死因子- α (tumor necrosis factor- α , TNF- α)、白细胞介素-1 β (interleukin-1 β , IL-1 β)、C反应蛋白(C-reactive protein, CRP)的下降也更加明显^[3]。

4 XOR抑制剂的抗破骨作用

骨免疫失调和病理性骨改建导致牙槽骨破坏是牙周炎的主要特征。一方面,牙周微生物失调导致免疫细胞的核因子 κ B受体活化因子配体(receptor activator of nuclear factor- κ B ligand, RANKL)增多,通过骨基质信号通路激活破骨细胞,降解骨基质。另一方面,成骨细胞和牙周韧带细胞受炎症刺激,骨保护素(osteoprotegerin, OPG)生成减少,骨免疫环境失调,进一步促进破骨细胞生成^[18]。一项临床研究中,高尿酸血症患者龈沟液的血尿酸水平会随着血尿酸的升高而升高,高尿酸组($n=29$)的血尿酸值与附着丧失呈显著正相关性,其中无症状高尿酸组($n=11$)龈沟液中尿酸和OPG的浓度显著高于正常对照组,痛风患者组($n=18$)龈沟液中RANKL的均值明显高于对照组^[19]。XOR抑制剂主要抑制破骨细胞活性,也可影响成骨细胞活性。在一项体外实验中发现,非布司他可阻断破骨细胞的RANKL信号通路,在60 μ mol/L的浓度下抑制小鼠白血病病毒诱导的单核巨噬细胞向破骨细胞分化^[20]。另一项大鼠体内实验中,36只通过手术制造颅骨缺损的大鼠分为了对照组、骨移植组、骨移植+别嘌呤醇组(腹腔注射别嘌呤醇

50 mg/d),发现别嘌呤醇可抑制颅骨的破骨细胞活性,减少炎性骨吸收,增加骨细胞中骨桥蛋白的表达^[21]。

5 XOR抑制剂对感染性疾病的治疗作用

XOR抑制剂在治疗COVID-19上显示出积极作用。在控制COVID-19患者的发热、咳嗽、呼吸急促、呼吸困难和肺部病损方面,非布司他(80 mg/d, 5 d)表现出与羟氯喹相似的治疗效果^[22]。非布司他和别嘌呤醇的免疫调节和抗炎作用可抑制炎症因子风暴的启动,从而预防COVID-19患者的严重急性呼吸道疾病,改善患者的预后^[23]。此外,别嘌呤醇已被批准用于儿童的呼吸道合胞病毒感染,其可能机制在于别嘌呤醇抑制淋巴细胞形成、XOR活性,抑制炎症因子释放^[23]。对于晚期慢性肾病患者,感染后菌血症、败血症相关死亡的风险较高,而非布司他(危险比0.93, 95% CI 0.87 ~ 0.99)和别嘌呤醇(危险比0.92, 95% CI 0.86 ~ 0.99)使用者的败血症/感染风险降低,使用非布司他还显著降低败血症/感染相关的死亡风险(危险比0.68, 95% CI 0.52 ~ 0.87)^[24]。

6 XOR抑制剂对炎症性疾病的治疗作用

XOR抑制剂在治疗心血管疾病、慢性肾脏病、糖尿病肾病等炎症性疾病上显示出积极作用。非布司他(≤ 40 mg/d, 36个月)可降低心血管疾病患者的心脑血管和肾脏事件(危险比0.601, 95% CI 0.384 ~ 0.940)和全因素死亡率(危险比0.160, 95% CI 0.047 ~ 0.547)的风险^[25]。对于慢性肾病,非布司他(从20 ~ 40 mg/d开始,根据血清尿酸浓度调整剂量,最大剂量至80 mg/d)可显著降低患者的血尿酸水平,减缓肾病进展^[22]。在伴高尿酸血症的糖尿病肾病患者中,非布司他(40 mg/d)治疗6个月可控制患者的血尿酸水平,改善肾小球滤过率^[26]。Meta分析显示,口服别嘌呤醇可有效降低糖尿病患者的血尿酸水平,保护肾功能^[27]。鉴于牙周炎是一种典型的系统性炎症性疾病,且与上述多种炎症性疾病存在双向联系,XOR抑制剂可能直接抑制牙周炎症或通过改善全身性炎症间接改善牙周炎。

7 XOR抑制剂对溶骨性疾病的治疗作用

别嘌呤醇、非布司他为痛风患者降尿酸治疗的一线用药。在痛风的慢性治疗和预防上别嘌呤

醇和非布司他均能发挥很好的作用,降低患者的血清尿酸水平,防止痛风的急性发作^[28]。一项旨在探究高尿酸血症对牙槽骨成骨与破骨活性影响的研究表明,与血尿酸正常组相比,高尿酸血症患者龈沟液中尿酸、OPG的浓度显著增加。高尿酸血症组的龈沟液中尿酸浓度、RANKL、RANKL/OPG与血清尿酸水平呈明显的正相关,龈沟液中尿酸浓度与OPG的浓度呈负相关^[19]。鉴于牙周炎也是一种溶骨性疾病,以及XOR抑制剂对其他溶骨性疾病的积极作用,XOR抑制剂可能对牙周炎有治疗作用。

8 XOR抑制剂对肠道和牙周微生态失调的作用

肠道菌群参与嘌呤代谢和尿酸的生成和降解。在门水平上,厚壁菌门和拟杆菌门占95%以上。与高尿酸血症小鼠模型组对比,别嘌呤醇治疗组改变了小鼠肠道菌群的相对丰度,如厚壁菌门下降,拟杆菌门增加^[29]。与高尿酸血症大鼠模型组相比,别嘌呤醇治疗组呈现出双歧杆菌属增加和阿德勒克氏厌氧菌属减少。另外,肠道微生物群可以将核苷酸转化为尿酸,并通过离子偶联转运蛋白将尿酸排泄到细菌细胞外,别嘌呤醇可抑制核苷酸代谢和减少离子偶联转运蛋白,可能有利于减少肠道尿酸^[30]。在肠道菌群多样性和功能特征方面,痛风患者与健康对照有显著差异,而非布司他治疗组更接近健康对照。与未治疗组相比,治疗组表现出双歧杆菌增多、中间普氏菌减少^[31]。肠道菌群通过参与嘌呤和尿酸的分解代谢来影响血尿酸水平。未治疗组的肠道菌群代谢能力明显低于健康对照组,导致尿酸积聚,这可能与痛风患者的肠杆菌减少有关,而治疗组与健康对照组无明显差异^[31-32]。综上,以别嘌呤醇和非布司他为代表的XOR抑制剂对调节肠道菌群组成及其嘌呤代谢有帮助,从而减少尿酸积聚。

与健康对照组相比,痛风患者唾液中的牙周致病菌(中间普氏菌)成分增加,提示痛风性高尿酸血症可能导致牙周微生态失调^[33]。反之,XOR抑制剂通过降低全身尿酸水平,有可能恢复牙周微生态的稳态,以下证据支持这一观点。第一,痛风患者长期服用别嘌呤醇后,有牙石减少的现象^[34]。第二,从代谢的角度,牙周炎是代谢物交换、菌群-宿主相互作用等过程失调的结果。宿主体内嘌呤核苷酸的分解,可为细菌成分的生物合成提供原料,包括嘌呤和尿酸。牙周炎患者的菌

斑中可富集到嘌呤代谢异常及嘌呤核苷酸合成的转录活性改变^[35]。许多G⁺和G⁻细菌本身也会产生嘌呤降解酶,这可能会加速宿主体内嘌呤的分解^[36]。因此,XOR抑制剂可能通过抑制细菌的嘌呤降解酶活性或刺激宿主的嘌呤回收途径,减少宿主体内的嘌呤分解^[37]。第三,别嘌呤醇可以抑制牙龈卟啉单胞菌诱导下引起的巨噬细胞XOR活性增加^[8]。第四,牙周微生态失调可能与肠道菌群失调有关,益生菌疗法可以减少结扎引起的牙周组织破坏^[38]。综上,XOR抑制剂有可能阻断牙周菌群对嘌呤的分解和利用过程,从而改善牙周微生态失调。

9 展望

为验证XOR抑制剂作为牙周炎辅助性治疗药物的疗效,有必要进行一系列临床研究,包括队列研究和随机对照试验。同时,还需开展实验性研究,来探索其发挥作用的潜在生物学机制。在用于牙周炎的临床治疗之前,也需优化XOR抑制剂的选择类型(别嘌呤醇或非布司他)、剂量、剂型(固体、凝胶或溶液)及给药途径(漱口或龈下冲洗)。还应注意,XOR是一种多功能酶,不只是具有负面功能,也有积极作用。例如,XOR可能具有抗菌作用、通过硝酸盐还原酶活性产生一氧化氮的作用^[39]。同理,尿酸在生理条件下也具有一定的抗氧化作用^[40]。因此,XOR抑制剂有可能干扰XOR的积极作用。同时,XOR抑制剂别嘌呤醇和非布司他的罕见却严重的副作用,如过敏反应和心血管事件等,也不应忽视^[10,41]。可见,XOR抑制剂通过牙周治疗特有的局部给药方式,如漱口或牙周袋内缓释控释系统,可最小化其潜在的副作用。

综上,XOR抑制剂(特别是别嘌呤醇和非布司他),可抑制炎症反应、氧化应激和破骨作用,有望作为免疫调节剂用于牙周炎的辅助治疗,其有效性和安全性仍有待临床研究验证。

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